JAMA | Review

Acute Cholecystitis
A Review

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IMPORTANCE Gallbladder disease affects approximately 20 million people in the US. Acute cholecystitis is diagnosed in approximately 200 000 people in the US each year.

OBSERVATIONS Gallstone-associated cystic duct obstruction is responsible for 90% to 95% of the cases of acute cholecystitis. Approximately 5% to 10% of patients with acute cholecystitis have *acalculous cholecystitis*, defined as acute inflammation of the gallbladder without gallstones, typically in the setting of severe critical illness. The typical presentation of acute cholecystitis consists of acute right upper quadrant pain, fever, and nausea that may be associated with eating and physical examination findings of right upper quadrant tenderness. Ultrasonography of the right upper quadrant has a sensitivity of approximately 81% and a specificity of approximately 83% for the diagnosis of acute cholecystitis. When an ultrasound result does not provide a definitive diagnosis, hepatobiliary scintigraphy (a nuclear medicine study that includes the intravenous injection of a radiotracer excreted in the bile) is the gold standard diagnostic test. Following diagnosis, early (performed within 1-3 days) vs late (performed after 3 days) laparoscopic cholecystectomy is associated with improved patient outcomes, including fewer composite postoperative complications (11.8% for early vs 34.4% for late), a shorter length of hospital stay (5.4 days vs 10.0 days), and lower hospital costs. During pregnancy, early laparoscopic cholecystectomy, compared with delayed operative management, is associated with a lower risk of maternal-fetal complications (1.6% for early vs 18.4% for delayed) and is recommended during all trimesters. In people older than 65 years of age, laparoscopic cholecystectomy is associated with lower mortality at 2-year follow-up (15.2%) compared with nonoperative management (29.3%). A percutaneous cholecystostomy tube, in which a drainage catheter is placed in the gallbladder lumen under image guidance, is an effective therapy for patients with an exceptionally high perioperative risk. However, percutaneous cholecystostomy tube placement in a randomized trial was associated with higher rates of postprocedural complications (65%) compared with laparoscopic cholecystectomy (12%). For patients with acalculous acute cholecystitis, percutaneous cholecystostomy tube should be reserved for patients who are severely ill at the time of diagnosis; all others should undergo a laparoscopic cholecystectomy.

CONCLUSIONS AND RELEVANCE Acute cholecystitis, typically due to gallstone obstruction of the cystic duct, affects approximately 200 000 people in the US annually. In most patient populations, laparoscopic cholecystectomy, performed within 3 days of diagnosis, is the first-line therapy for acute cholecystitis.

JAMA. 2022;327(10):965-975. doi:10.1001/jama.2022.2350

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Section Editor: Mary McGrae McDermott, MD, Deputy Editor.

Acute cholecystitis is an acute inflammatory disease of the gallbladder that is caused by gallstone obstruction of the cystic duct in approximately 90% to 95% of people diagnosed with this condition.[1] Less commonly, acalculous cholecystitis, in which acute inflammation of the gallbladder develops without gallstones, is present in approximately 5% to 10% of people diagnosed with acute cholecystitis.

Gallbladder disease affects approximately 20 million individuals in the US and results in estimated direct annual costs of more than $6.3 billion, with more than 200 000 people diagnosed with acute cholecystitis each year.[2-4] Of the 10% to 15% of adults in the US general population with cholelithiasis, approximately 80% are asymptomatic.[5] Twenty percent of patients with gallstones will eventually develop gallstone-related complications at an incidence rate of 1% to 4% annually, with calculous acute cholecystitis as the first clinical presentation in 10% to 15% of all patients with gallstones.[6]

In contrast, the etiology of *acalculous acute cholecystitis*, defined as an acute inflammatory disease of the gallbladder in the absence of cholelithiasis, is multifactorial. Factors associated with acalculous acute cholecystitis include critical illness, diabetes, HIV infection, atherosclerosis, and total parenteral nutrition.[7,8] Acalculous acute cholecystitis is present in approximately 5% to 10% of patients presenting with acute cholecystitis. Acalculous

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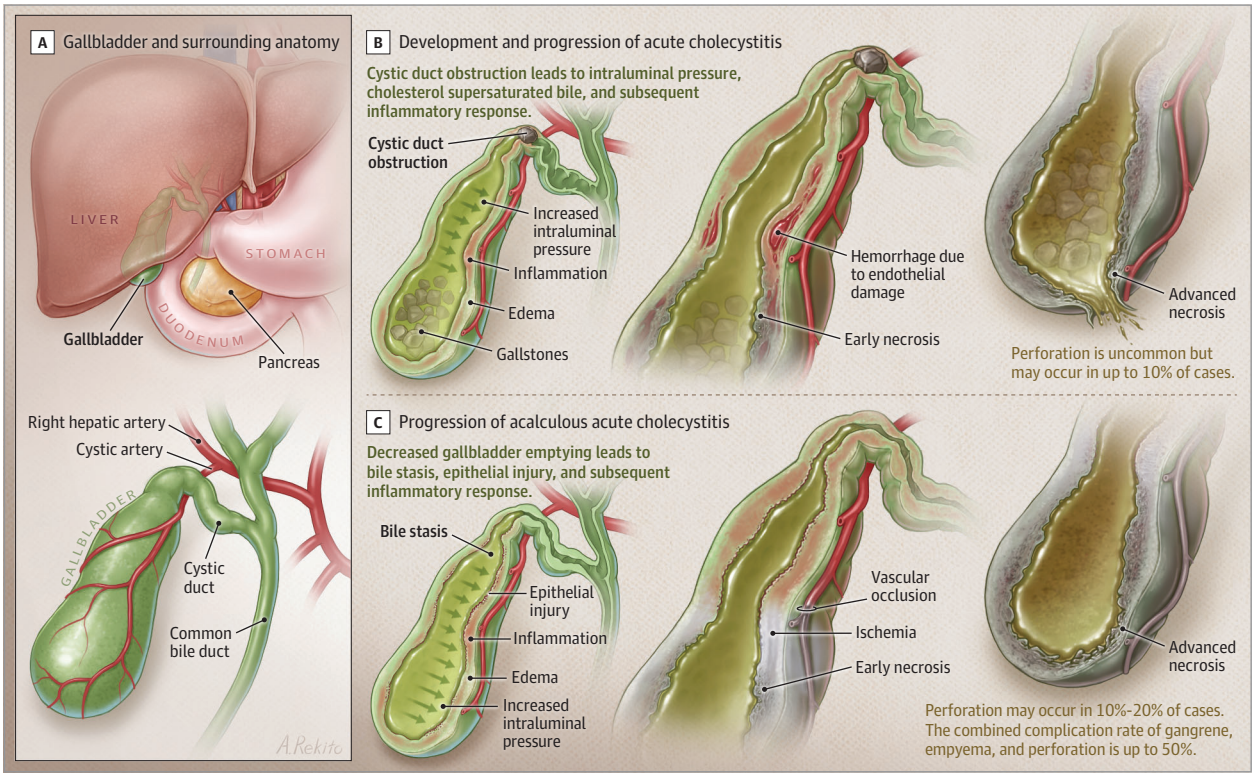
Figure. Progression of Acute Cholecystitis



acute cholecystitis occurs in about 0.2% to 0.4% of all critically ill patients, usually in patients aged 50 years or older, and is at least 3 times more common in men than women.[9-11]

Methods

The PubMed and Cochrane databases were used to search for English-language reports related to acute cholecystitis, including studies focused on risk factors, pathogenesis, diagnosis, and treatment that were published between January 1, 2000, and December 31, 2021. Seminal studies published before 2000 were included when relevant to the review and when more recent data were unavailable.

A total of 4802 studies were identified. We prioritized randomized clinical trials, meta-analyses, systematic reviews, national or international guidelines, population-based studies, and observational studies. A total of 102 studies were included, consisting of 4 randomized clinical trials, 6 meta-analyses, 5 systematic reviews, 7 national or international guidelines, 30 population-based studies, and 50 observational (cross-sectional) studies.

Risk Factors

Cholelithiasis is the most common risk factor for acute cholecystitis. People from Central and South America who have Hispanic ethnicity and individuals with American Indian ancestry have the highest prevalence of cholelithiasis.[2,12] The age- and sex-adjusted global prevalence of cholelithiasis is approximately 35% in Mapuche Indian individuals and 27% in Hispanic individuals.[13] In contrast, the prevalence of cholelithiasis among individuals from sub-Saharan Africa is approximately 5% and the prevalence is approximately 3.2% to 15.6% in Asia.[14,15]

In the US, the age-standardized prevalence of gallbladder disease was estimated based on a sample of more than 14 000 persons aged 20 to 74 years in whom gallstones were detected by ultrasonography or after cholecystectomy. The gallbladder disease prevalence was 8.6% among non-Hispanic White men and 16.6% among non-Hispanic White women, 8.9% among Mexican American men and 26.7% among Mexican American women, and 5.3% among non-Hispanic Black men and 13.9% among non-Hispanic Black women.[2] Risk factors for gallbladder disease, such as obesity, weight loss, pregnancy, and drinking less than 1 or 2 alcoholic drinks per day (7-14 g/d), do not explain the differences in the racial or ethnic prevalence of cholelithiasis.[16]

Genetic markers have not been shown to explain the differences in risk among racial and ethnic groups. Other factors, such as a diet high in fat or low in fiber, may explain a more significant fraction of the attributable risk associated with cholelithiasis.[17] Although gallstones are 2 to 3 times more common in women, this difference tends to diminish with older age, and the risk of developing cholelithiasis increases with age.[6] The pathophysiological basis for the increasing prevalence of gallstone disease in older people is unclear.

Congenital hemolytic anemias, especially thalassemia and sickle cell disease, are a common cause of gallstones, particularly in children.[18] A university-based study in Brazil of 107 patients that evaluated cholelithiasis in patients with sickle cell disease showed a prevalence of 4.4% in patients younger than 10 years,

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35.4% in patients aged 11 to 29 years, and 18.2% in patients aged 30 years or older.[19]

Pregnancy increases stone and sludge formation. Sludge consists of a suspension of mucus, cholesterol, and calcium salts formed within the gallbladder and affects 5.1% of pregnant people during the second trimester, 7.9% during the third trimester, and 10.2% at 4 weeks' to 6 weeks' postpartum.[20,21]

Obesity is also a risk factor for cholelithiasis. In a US study of 13 962 participants in the third National Health and Nutrition Examination Survey, women who had gallstones had a higher mean body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) compared with those without gallstones (29.7 vs 25.9, respectively), whereas men with gallstones had a mean BMI of 28.3 vs 26.5 those without gallstones.[22] Substantial weight loss, particularly after bariatric surgery, is associated with the development of gallstones.[23] A retrospective analysis of 586 patients (75.7% female) who underwent bariatric surgery showed that among patients who developed symptomatic gallstones postoperatively, 91.3% had lost greater than 25% of their body weight.[24]

Some medications, such as octreotide (incidence rate of 5%-66% after long-term use [>1 month]) and ceftriaxone (incidence rate of 8.8% after 10 doses), are associated with an increased rate of gallstone formation.[25,26] Calculous acute cholecystitis is also more common in people with diabetes.[27] The incidence rate per 10 000 person-years for people with type 2 diabetes was 51.6 vs 35.5 for those without type 2 diabetes.[28] In a population-based study of 71 369 participants, the use of glucagon-like peptide analogues to treat type 2 diabetes (such as exenatide or liraglutide) was associated with an increased risk of bile duct and gallbladder disease vs the concurrent use of at least 2 oral antidiabetes drugs (6.1 vs 3.3 per 1000 person-years, respectively).[29]

In studies of specific patient populations, risk factors for acalculous acute cholecystitis included critical illness (0.2%-0.4%), severe trauma (10%), burns (0.4%-3.5%), cardiac surgery with cardiopulmonary bypass (0.08%), and total parenteral nutrition (16%). In patients undergoing bone marrow transplant, the incidence of acalculous acute cholecystitis was as high as 4%.[30-34]

Pathogenesis

Acute cholecystitis due to gallstones occurs after a cystic duct obstruction caused by gallstones or sludge or lithogenic bile.[35] The degree and duration of the cystic duct obstruction determine the rate of progression to acute cholecystitis and the severity of gallbladder inflammation. Cystic duct obstruction increases intraluminal pressure within the gallbladder and, together with cholesterol-supersaturated bile, initiates an acute inflammatory response. Secondary bacterial infections with enteric organisms (most commonly *Escherichia coli*, *Klebsiella,* and *Streptococcus faecalis*) occur in about 20% of patients with acute cholecystitis.[36]

Acute cholecystitis progresses in 3 distinct phases after a cystic duct obstruction. The first phase is characterized by inflammation and is manifest by gallbladder wall congestion and edema (occurs 2-4 days after the onset of symptoms). The second phase is characterized by hemorrhage and necrosis of the gallbladder wall, which may lead to gallbladder perforation at the site of ischemic gangrene and subsequent biliary peritonitis (occurs 3-5 days after symptom onset). The third phase, the chronic or purulent phase, is characterized by leukocyte infiltration, necrotic tissue, and suppuration along with intraluminal pus and gross infection (occurs on day 6 or later after symptom onset) (**Figure**).

After this acute phase, intraluminal purulence is replaced with granulation tissue and progresses to subacute cholecystitis and eventually chronic cholecystitis.[37] In contrast, the pathogenesis of acalculous acute cholecystitis is multifactorial and likely results from bile stasis or ischemia of the gallbladder wall. Bile stasis can be caused by fasting or ileus, leading to bile inspissation that is directly toxic to the gallbladder epithelium.[38] Microvascular occlusion of the gallbladder vasculature occurs secondary to endothelial injury, leading to gallbladder ischemia in the setting of hypoperfusion, which may occur in critically ill patients.[1] Acalculous acute cholecystitis can also progress to gangrene, gallbladder empyema, and perforation in up to 50% of patients.[10]

Box. Diagnostic Criteria for Acute Cholecystitis Based on 2018 Tokyo Guidelines

Local Signs of Inflammation
- Murphy sign
- Right upper quadrant mass, pain, or tenderness

Systemic Signs of Inflammation
- Fever
- Elevated C-reactive protein level
- Elevated white blood cell count

Imaging Findings Characteristic of Acute Cholecystitis
- Suspected diagnosis: 1 local sign plus 1 systemic sign
- Definite diagnosis: 1 local sign plus 1 systemic sign plus 1 image finding characteristic of acute cholecystitis

Adapted from Yokoe et al.[42]

Diagnosis

Acute cholecystitis should be suspected in patients presenting with constant right upper quadrant pain with or without an association with eating. Fever, nausea, and vomiting are the typical presenting symptoms. In a 2017 systematic review that included 3 observational studies, the sensitivity for fever was 31% to 62%.[39] On physical examination, right upper quadrant tenderness associated with localized peritonitis was present in 95.7% of patients.[40] Murphy sign (arrest of inspiration during palpation of the right upper quadrant due to pain) is pathognomonic of acute cholecystitis. Murphy sign has a sensitivity of 62% and a specificity of 96% for acute cholecystitis.[39] Patients typically have leukocytosis with left shift and immature bands.

In severe acute cholecystitis, mild jaundice (serum concentrations of bilirubin <3 mg/dL [to convert to μmol/L, multiply by 17.104]) may be present and caused by inflammation around the biliary tract or by direct pressure on the biliary tract from the distended gallbladder, which obstructs the biliary tree.[1] No single clinical finding or laboratory test is sufficient to establish or exclude cholecystitis without further testing.[41] Recommended laboratory studies in the workup for acute cholecystitis should include a complete blood cell

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Table 1. Characteristics of Diagnostic Tests Available for Acute Cholecystitis

Diagnostic test	Findings for diagnosis of acute cholecystitis	Diagnostic accuracy for acute cholecystitis	Advantages of diagnostic test	Appropriate population
Ultrasonography of the right upper quadrant	• Gallstones or sludge • Pericholecystic fluid • Gallbladder distention • Edematous or thickened gallbladder wall	• Sensitivity: 81% • Specificity: 83%[46]	• Inexpensive • Readily available • No radiation exposure	• Patients with right upper quadrant pain • Use should be limited in patients with morbid obesity
Computed tomography	• Gallbladder distention • Gallbladder wall thickening • Pericholecystic fat stranding • Pericholecystic fluid	• Sensitivity: 94% • Specificity: 59%[46] • 20% of gallstones are not detectable on scan[47]	• Able to assess other causes of abdominal pain	• Diffuse abdominal pain or uncharacteristic history
Hepatobiliary scintigraphy (hepatic iminodiacetic acid scan)	• Absent uptake of radiotracer into the gallbladder before and after morphine administration	• Sensitivity: 96% • Specificity: 90%[46]	• The most sensitive and specific test for acute cholecystitis	• Reserved for patients with a prior nondiagnostic ultrasound result
Magnetic resonance imaging and magnetic resonance cholangiopancreatography	• Gallstones (often obstructing the neck) • Gallbladder wall thickening (>3 mm) • Gallbladder wall edema • Gallbladder distention (>40 mm) • Pericholecystic fluid • Fluid around the liver	• Sensitivity: 88% • Specificity: 89%[48]	• Able to evaluate potential complications of cholecystitis and evaluate for concurrent choledocholithiasis	• Reserved for patients with suspected choledocholithiasis or biliary injury

count and serum chemistry panel, including a liver function test, bilirubin level, and serum lipase level (to rule out acute pancreatitis in the differential diagnosis), in addition to chest radiography and electrocardiography.

The diagnostic criteria for acute cholecystitis according to the Tokyo guidelines[42,43] are outlined in the **Box**. In small studies including fewer than 200 patients, the sensitivity of these criteria was estimated to be between 83% and 85% with the specificity estimated between 37% and 50%.[44,45]

Diagnostic Studies

Right Upper Quadrant Ultrasonography

Ultrasonography is the initial imaging modality of choice for evaluating suspected acute cholecystitis due to its relatively low cost, easy accessibility, short examination duration, and absence of ionizing radiation (**Table 1**). Sonograms typically show pericholecystic fluid (fluid around the gallbladder), gallbladder distention, an edematous gallbladder wall, and gallstones or sludge if present. A 2012 meta-analysis of 5859 patients with acute cholecystitis reported that ultrasonography was associated with a sensitivity of 81% and a specificity of 80% for acute cholecystitis.[46]

In a study of 189 patients with suspected calculous acute cholecystitis, the presence of gallstones and a positive ultrasonographic Murphy sign (maximal abdominal tenderness when the ultrasound probe is applied over the gallbladder) had a sensitivity of 48% for acute cholecystitis. The specificity for acute cholecystitis in patients with a negative Murphy sign was 96%. Bedside ultrasonography by nonradiologists, particularly among clinicians in the emergency department for the diagnosis of acute cholecystitis, is increasingly used as a diagnostic test. In a study of 1690 patients, bedside ultrasonography performed by emergency department physicians had a sensitivity of 88% (95% CI, 84%-91%) and a specificity of 87% (95% CI, 82%-91%) using radiological interpretation as the criterion reference.[49]

Computed Tomography

The computed tomographic (CT) scan characteristics associated with uncomplicated acute cholecystitis include distension of the gallbladder, mural thickening, pericholecystic fat stranding, and pericholecystic fluid.[50] Gallstone detection with a CT scan is dependent on the composition of the gallstones and the thickness of CT slices. At least 20% of gallstones have similar attenuation as bile and are not detectable with CT.[47] A 2012 meta-analysis of 5859 patients reported an estimated sensitivity of 94% and a specificity of 59% for CT in the diagnosis of acute cholecystitis.[46]

Hepatobiliary Scintigraphy (Hepatic Iminodiacetic Acid Scan)

Hepatobiliary scintigraphy, also known as the hepatic iminodiacetic acid scan, is a nuclear medicine diagnostic test in which technetium-labeled analogue iminodiacetic acid (radiotracer) is intravenously injected. The radiotracer is excreted into the bile.[51,52] Patients should fast for at least 4 hours to 6 hours before radiotracer injection. Administration of a subanalgesic dose of morphine causes sphincter of Oddi contraction, thus diverting incoming bile to the gallbladder. In patients with a patent cystic duct, gallbladder filling will be visible within 30 minutes of morphine administration.

Continued nonvisualization of the gallbladder after delayed images or morphine augmentation confirms cystic duct obstruction. Hepatobiliary scintigraphy has a sensitivity of 96% and a specificity of 90% for acute cholecystitis.[46] Ultrasonography is preferred as the initial diagnostic test and hepatobiliary scintigraphy is reserved for the 20% of patients with equivocal ultrasonography test results. Hepatobiliary scintigraphy is the most reliable imaging study for patients with suspected acalculous acute cholecystitis.[30]

Magnetic Resonance Imaging and Magnetic Resonance Cholangiopancreatography

Magnetic resonance imaging findings of acute uncomplicated cholecystitis include (1) gallstones (often impacted in the gallbladder neck or cystic duct), (2) gallbladder wall thickening (>3 mm), (3) gallbladder wall edema, (4) gallbladder distention (diameter >40 mm),

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Table 2. Summary of Treatment Options for Acute Cholecystitis

Disease process	Disease process definition	Treatment options	Additional information	Adverse events associated with treatment
Uncomplicated calculous acute cholecystitis	Acute inflammation of the gallbladder due to cystic duct obstruction by a gallstone without abscess, perforation, or gangrene	Laparoscopic cholecystectomy	• Should be performed early (1-3 d) after diagnosis • Available for pregnant patients (during any trimester) • Older patients have better clinical outcomes with laparoscopic cholecystectomy vs nonoperative management • Should be offered to patients with mild to moderate liver cirrhosis	• Common bile duct injury: 0.4%-0.6% of cases[56,57] • Infectious or bleeding complications: 1%-2% of cases[56]
		Combination ampicillin and sulbactam or combination piperacillin and tazobactam	• Antibiotics should be used before and at the time of surgery • Not indicated postoperatively	
Complicated calculous acute cholecystitis	Acute inflammation of the gallbladder due to cystic duct obstruction by a gallstone with abscess, perforation, or gangrene	Laparoscopic vs open cholecystectomy	• Should be performed early to obtain source control	• Common bile duct injury: 0.4%-0.6% of cases[56,57] • Infectious or bleeding complications: 1%-2% of cases[56]
		Subtotal cholecystectomy	• Available when the gallbladder cannot be safely removed • A gallbladder fossa drain should be left postoperatively	• Cystic duct leak: 18% of cases[58,59] • Postoperative abscess: 5%-6% of cases[58] • Recurrent biliary event: 9%-18% of cases[60]
		Combination ampicillin and sulbactam or combination piperacillin and tazobactam	• Antibiotics should be used before and at the time of surgery • Continue a 4- to 7-d course postoperatively in patients without adequate source control or signs of sepsis	
Acalculous acute cholecystitis	Acute inflammation of the gallbladder without gallstones	Laparoscopic vs open cholecystectomy	• In patients with acceptable perioperative risk, should proceed with early cholecystectomy	• In critically ill patients, higher composite postoperative complications vs percutaneous cholecystostomy tube (8% vs 5%)[61]
		Percutaneous cholecystostomy tube	• Reserved for patients with exceptionally high perioperative risk or severe critical illness • Uncommonly used for patients with calculous cholecystitis	• Mortality: 4.7% vs 1.2% for cholecystectomy • Bleeding: 17.1% vs 9.5% for cholecystectomy • Infection:13.3% vs 4.5% for cholecystectomy[62]

(5) pericholecystic fluid, and (6) fluid around the liver.[53] The presence of 1 or more of these 6 findings indicates acute cholecystitis, yielding a sensitivity of 88% and a specificity of 89%.[48] Magnetic resonance imaging can also be used to evaluate potential complications of acute cholecystitis such as gangrenous, emphysematous, and perforated cholecystitis. Furthermore, magnetic resonance imaging and, specifically, magnetic resonance cholangiopancreatography allow the exclusion of concurrent choledocholithiasis in the setting of cholecystitis, which can assist in the planning of the therapeutic approach.[54,55]

Differential Diagnosis

Acute cholecystitis must be differentiated from other diseases that cause right upper quadrant abdominal pain and nausea or vomiting, such as biliary colic and acute cholangitis. The term *biliary colic*, consisting of abdominal pain due to a blocked cystic duct is a misnomer. Biliary colic presents with intense, constant right upper quadrant pain in the absence of fever and leukocytosis. This pain is not intermittent or colicky as is often assumed, but relatively constant due to the cystic ductal obstruction, and the pain only dissipates after the gallstones fall back into the gallbladder.[5] Biliary colic typically appears within a couple of hours after eating a meal and improves within a few hours. The gallbladder wall is within normal limits on the ultrasound without any evidence of pericholecystic fluid.

Acute cholangitis is defined by fever, jaundice, and right upper quadrant pain with the ultrasound revealing dilated intrahepatic and extrahepatic biliary ducts. Other diagnoses to consider in a patient presenting with symptoms of acute cholecystitis include acute gastritis, peptic ulcer disease, hiatal hernia, acute pancreatitis, acute viral hepatitis, acute appendicitis, and myocardial infarction.

Treatment

The standard treatment for calculous acute cholecystitis is cholecystectomy (**Table 2**). In the US, laparoscopic cholecystectomy is the standard of care.[63-65]

Early vs Delayed Cholecystectomy

A 2013 open-label randomized clinical trial (n = 618) compared patients with acute cholecystitis undergoing surgery within 24 hours of admission vs patients first treated with antibiotics before undergoing cholecystectomy between 7 and 45 days after initial admission. The study found a much lower prevalence of postoperative complications within the first 75 days in the group treated with early cholecystectomy (11.8% for patients treated within 24 hours of admission vs 34.4% for those treated 7-45 days after initial admission; $P < .001$). Early cholecystectomy was also associated with a shorter mean hospital length of stay (5.4 days for patients treated within 24 hours of admission vs 10.0 days for those treated 7-45 days after initial admission; $P < .001$) and lower total hospital costs (€2919 vs €4262, respectively; $P < .001$).[66]

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A review of 15 760 Swedish patients with acute cholecystitis showed that bile duct injury after surgery was lower for patients who underwent cholecystectomy within 4 days of admission (0.17% vs 0.53% for those who underwent cholecystectomy after >4 days; $P = .008$) and that patients also had a lower rate of death within 30 days when patients underwent cholecystectomy within 2 days of admission compared with more than 2 days after admission (0.39% vs 1.33%, respectively; $P = .004$).[67] A 2015 observational study of 45 452 patients from France showed that intensive care admission, reoperation, and postoperative sepsis were lower for patients who underwent surgery between 1 and 3 days after admission than patients who underwent surgery later. Mortality was also lower for patients who underwent cholecystectomy between days 1 and 3 than for patients who underwent cholecystectomy on day 5 (1.0% vs 1.9%, respectively; $P < .001$).[68]

In 2020, a review of more than 100 000 cholecystectomies in New York State found that patients who underwent cholecystectomy less than 72 hours from admission had a lower conversion to an open procedure (7.5% vs 13.8% who underwent cholecystectomy >72 hours after admission; $P < .001$).[69] However, these results may have been influenced by confounding if healthier patients were more likely to undergo an earlier operation. In addition, evidence from 243 536 patients in the US Nationwide Inpatient Sample database showed that non-White patients had higher rates of emergent admission compared with White patients (84% vs 78%, respectively; $P < .001$), suggesting there are disparities in health care access for non-White patients who have acute cholecystitis.[70] In summary, early cholecystectomy was associated with significantly better outcomes than delayed cholecystectomy.[66-69]

Approximately 2% to 15% of patients undergoing laparoscopic cholecystectomy must be converted to open cholecystectomy. This phenomenon occurs when a safe surgical dissection is not possible during the laparoscopic procedure.[71] A 2017 systematic review of 30 observational and mostly retrospective studies found that while the data quality was poor with a high probability of bias, most studies showed that male sex, older age, high BMI, and the presence of acute cholecystitis were associated with higher rates of conversion to an open procedure.[72] One single-center, longitudinal observational study of 732 patients reported several variables with a significant association with conversion from laparoscopic to open cholecystectomy: previous upper abdominal surgery (11% vs 0.8% in those undergoing laparoscopic cholecystectomy), BMI greater than 30 (55% vs 18%), impacted gallstone at the gallbladder neck (51% vs 16%), and gallbladder wall thickness greater than 3 mm (38% vs 0.4%).[73]

Postoperative Complications After Cholecystectomy

A 2011 analysis of a Swiss national database of 4113 patients (median age, 59.8 years; 52.8% female) who underwent laparoscopic cholecystectomy for acute cholecystitis reported that 6.1% of patients had a postoperative complication.[56] The most common complications were abdominal wall or intra-abdominal bleeding (1.8%) and superficial wound infection (1.0%). Extrahepatic bile duct injury occurred in 17 patients (0.4%). In a 2021 analysis of the US National Readmissions Database, including 1 768 725 patients who underwent laparoscopic cholecystectomy, 0.46% of patients required a bile duct injury repair.

Biliary duct injury during surgery typically manifests with jaundice and fever postoperatively and is typically diagnosed intraoperatively or within a few days postoperatively. Even though the surgeon can manage most bleeding or infectious complications, concern for a biliary injury requires prompt diagnosis and management by a surgeon with expertise in hepatobiliary reconstruction. The evaluation for postoperative jaundice should include liver function tests. Ultrasonography is a practical first test to assess fluid collection or enlarged biliary ducts. When evaluating for bile duct injury postoperatively, magnetic resonance cholangiopancreatography is more informative compared with CT and should be obtained in the setting of abnormal bilirubin levels or abnormal ultrasound findings.[74]

Acute Cholecystitis in Older Patients

Initial nonoperative management with delayed cholecystectomy has been evaluated as an alternative strategy to immediate cholecystectomy for older patients (aged >65 years).[75] However, data have consistently shown that outcomes following early laparoscopic cholecystectomy in octogenarians are comparable with younger patients.[76] A 2010 study using Medicare data examined 29 818 patients older than 65 years of age and reported that among patients who did not undergo initial cholecystectomy, 38% were readmitted for gallbladder-related complications, whereas the readmission rate was only 4% for those who underwent an initial cholecystectomy.

The absence of cholecystectomy during the initial hospitalization was associated with higher mortality at 2 years (29.3%) compared with patients who underwent a cholecystectomy during the initial hospitalization (15.2%) ($P < .001$).[77] A similar study from England analyzed 47 500 patients aged 80 years or older from a national hospital database. Although the study demonstrated high 30-day mortality in the early cholecystectomy cohort compared with the delayed cholecystectomy cohort (11.6% vs 9.9%, respectively), there was a more substantial increase in mortality at 1 year for patients who underwent delayed cholecystectomy (20.8 vs 27.1%; $P < .001$).[78] However, these observational studies are likely influenced by confounding, in which healthier patients were selected for early cholecystectomy.

Acute Cholecystitis During Pregnancy

Nongynecological surgery occurs in 1% to 2% of pregnant patients, and abdominal surgery, including cholecystectomy, comprises 45% of these surgeries.[79] Current guidelines from the American College of Obstetricians and Gynecologists and the Society of American Gastrointestinal and Endoscopic Surgeons recommend that laparoscopic cholecystectomy be performed for acute cholecystitis during any trimester in the presence of acute cholecystitis.[80,81] Despite these recommendations, national data from the US showed that approximately 60% of pregnant women with acute cholecystitis were managed nonoperatively.[82]

Recent data suggested that the risk associated with cholecystectomy was lower than the risk associated with nonoperative management of acute cholecystitis during pregnancy. A 2017 study of a national database in England included 47 628 pregnant patients undergoing nonobstetric surgery.[83] The estimated risk of nonobstetric surgery during pregnancy was relatively low, with 1 stillbirth occurring in 1 of every 287 surgical operations and 1 preterm delivery occurring in 1 of every 31 operations. Even though this

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study was observational and may not have accounted for significant confounding, it suggested that the rate of obstetric complications associated with surgery is low.

A 2021 study examined the US National Inpatient Sample and identified nearly 24 000 pregnant women diagnosed with acute cholecystitis. Among these patients, early laparoscopic cholecystectomy for acute cholecystitis was associated with lower preterm delivery, preterm labor, or spontaneous abortion when performed within 1 day of presentation compared with a delay of 7 days or longer (1.6% vs 18.4%, respectively; $P < .001$).[84] In summary, laparoscopic cholecystectomy should be recommended to pregnant women with acute cholecystitis regardless of trimester.

Acute Cholecystitis in Patients With Cirrhosis

In retrospective studies, the Child-Pugh score and the Model for End-stage Liver Disease (MELD) score are associated with outcomes prior to cholecystectomy in patients with acute cholecystitis. A 2010 retrospective study of 220 patients in Greece with cirrhosis and acute cholecystitis reported higher perioperative complications for patients with a Child-Pugh score of 10 to 15 (class C; decompensated disease) or a MELD score greater than 13 compared with more favorable scores (MELD score range, 6-40).[85] A more recent analysis of the American College of Surgeons National Surgical Quality Improvement database showed similar results and reported that higher MELD scores were associated with higher rates of postoperative complications (wound, infectious, or respiratory) and mortality. Among patients with MELD scores greater than 15, mortality rates were 3.2%.[86] The presence of ascites and a MELD score greater than 20 were associated with an even higher risk of postoperative complication after laparoscopic cholecystectomy (66.7%) or death (33.3%).

A 2021 study of 349 patients with cirrhosis who were US veterans reported lower postoperative complications (9.5% vs 31.5%; $P < .001$) and mortality (3.5% vs 11.9%; $P = .003$) among those who underwent laparoscopic vs open cholecystectomy.[87] Even though clinical trial data are lacking, the current evidence suggests that cholecystectomy is safer than nonoperative management for patients with a Child-Pugh scores of 5 to 6 (class A; well-compensated disease) or scores of 7 to 9 (class B; significant functional compromise) or those with a MELD score of less than 15.

However, evidence for these criteria is not well established, and clinicians must use additional clinical factors when considering risks in patients with cirrhosis and acute cholecystitis, such as age, other medical comorbidities, and the presence of ascites. When cholecystectomy is determined to be unsafe, internal drainage with endoscopic retrograde cholangiopancreatography or transduodenal drainage may be an alternative therapy, depending on the expertise of the available clinicians.[88,89]

Management of Complicated Cholecystitis

Acute, complicated cholecystitis is defined as cholecystitis with the presence of either gallbladder necrosis, perforation, pericholecystic abscess, or cholecystoenteric fistula. Patients with these complications are at higher risk for adverse outcomes after cholecystectomy. Even though antibiotic therapy should be initiated at the time of presentation, nonoperative management is not appropriate for these patients because antibiotics will be inadequate in the setting of necrotic tissue or abscess.

In most patients with complicated cholecystitis, laparoscopic cholecystectomy is a reasonable initial approach, but conversion to open cholecystectomy may be required. Inability to achieve a safe gallbladder dissection during laparoscopic or open cholecystectomy should prompt subtotal cholecystectomy, which consists of removing most of the gallbladder wall, gallstones, and closing the cystic duct orifice by fenestration.[90] An analysis of 290 855 patients from the Nationwide Inpatient Sample identified that among those who underwent subtotal cholecystectomy compared with total cholecystectomy there was an increased prevalence in use of subtotal cholecystectomy in men (68.2% vs 48.3% women; $P < .001$), in Asian patients (5.4% vs 2.4% for non–Asian patients; $P = .013$), and in patients with alcohol use disorder (4.9% vs 2.4% for patients without alcohol use disorder; $P < .018$).[91]

Few data are available regarding the appropriate management of cholecystoenteric fistula and potential gallstone ileus (a gallstone passed into the intestinal tract causing bowel obstruction). A 2020 case series of 15 patients with cholecystoenteric fistula reported high variability in the treatment strategy in that 5 patients underwent laparotomy and stone removal without repair of their fistula, 8 patients underwent an open cholecystectomy and repair after laparoscopic conversion, and 2 patients underwent a laparoscopic repair.[92]

Few studies have reported complication rates after open and laparoscopic subtotal cholecystectomy. A 2015 meta-analysis of 1228 patients from 30 studies that included both randomized and observational data showed a higher prevalence of bile leak (defined as a leak from the gallbladder remnant or cystic duct stump) after subtotal cholecystectomy in patients who did not have their cystic duct or gallbladder stump closed compared with those who did (42.0% vs 16.5%, respectively).[58] This review also reported that postoperative procedures were common in patients who underwent endoscopic retrograde cholangiopancreatography, which was required in 4.1% of patients who underwent subtotal cholecystectomy. An additional 1.8% of patients underwent reoperation for biliary complication (41%), abscess (23%), completion cholecystectomy (18%), bleeding (9%), or bowel obstruction (9%). A subhepatic abscess was present in 2.9% of patients, but only 5% underwent image-guided percutaneous drainage. Overall, evidence for the treatment of complicated cholecystitis supports the use of both open and laparoscopic subtotal cholecystectomy with gallbladder fossa drain placement due to the relatively high rate of bile leak.

Antibiotic Therapy

Acute cholecystitis is primarily an inflammatory process, but secondary bacterial infection of the gallbladder can occur due to cystic duct obstruction and bile stasis in up to 20% of patients.[1,36] Consequently, antibiotics to treat gram-negative and anaerobic organisms typically include combination ampicillin with sulbactam or combination piperacillin with tazobactam; these combination therapies should be administered prior to surgery to protect against sepsis and wound infection.

Even though the data are limited, the 2018 Tokyo guidelines recommend using antibiotics prior to and at the time of operative intervention for patients with uncomplicated cholecystitis.[93] Data for postoperative use suggest that routine postoperative antibiotics are not associated with improved outcomes. A 2014 trial of 414

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French patients randomized patients to either only preoperative amoxicillin plus clavulanic acid or an additional 5-day course postoperatively and showed no differences in infection rates after cholecystectomy at 17% for the nontreatment group and 15% for the extended postoperative antibiotic group (absolute difference, 1.93% [95% CI, −8.98% to 5.12%]).[94]

Similarly, a 2017 trial of 150 patients from the Netherlands randomized patients to either a single dose of preoperative cefazolin vs at least a 3-day course of cefuroxime plus metronidazole. There were no significant differences in infectious complications after cholecystectomy at approximately 4% for both groups (absolute difference, 0.2% [95% CI, −8.2% to 8.2%]).[95] Therefore, postoperative antibiotics should be considered only for patients with signs of residual infection or sepsis.[93]

Percutaneous Cholecystostomy Tube

In patients with acute cholecystitis and an exceptionally high perioperative risk, placing a percutaneous cholecystostomy tube (PCT) can be an alternative to cholecystectomy. Patients with increased perioperative risk include older patients with multiple medical comorbidities and critically ill patients at the time of diagnosis.[96] A PCT requires image-guided placement of a percutaneous drainage catheter into the gallbladder lumen.[97] A PCT decompresses the gallbladder while also draining infection and can improve cholecystitis, thereby allowing greater time to stabilize the patient prior to cholecystectomy. Despite evidence suggesting that PCT use has increased over the last 20 years, the best patient population to receive a PCT remains unclear.[98]

Compared with patients with acalculous acute cholecystitis, PCT use among patients with calculous cholecystitis has been controversial. A 2013 Cochrane Review of high-risk patients with calculous acute cholecystitis concluded that there was insufficient evidence to determine whether PCT improved outcomes.[99] Subsequently, a multicenter, randomized trial conducted in the Netherlands (CHOCOLATE trial[100]) compared laparoscopic cholecystectomy vs PCT in 142 patients with acute cholecystitis who were at increased risk for perioperative complications. The mean age was older than 70 years in both cohorts, diabetes was present in 20% to 24% of patients, and all patients had an Acute Physiology and Chronic Health Evaluation score of 7 or greater. The study was terminated early after a planned interim analysis showed higher significant complications (cardiopulmonary and infectious complications, need for reintervention, and recurrent biliary disease) among patients in the PCT group (65% vs 12% in those who underwent laparoscopic cholecystectomy; $P < .001$).

Similarly, a 2020 study of 358 624 patients that analyzed data from the US Nationwide Readmission Database found that among patients aged 65 years or older with evidence of end-organ dysfunction and acute cholecystitis, PCT was associated with increased mortality compared with laparoscopic cholecystectomy (16% vs 2%, respectively; $P < .001$), increased composite postoperative complications (60% vs 25%; $P < .001$), and longer length of stay (15 days vs 9 days; $P < .001$). However, the study did not differentiate between acalculous and calculous cholecystitis.[101]

For patients with acalculous acute cholecystitis, data regarding PCT are mixed. A large, multicenter database study of patients from California examined the association of PCT with outcomes among 1725 critically ill patients with acalculous cholecystitis.[61] Outcomes were significantly improved for patients who underwent PCT placement compared with those who underwent laparoscopic or open cholecystectomy, including lower composite postoperative complications (5.0% vs 8.0%, respectively; $P < .05$) and decreased hospital costs ($40 516 vs $51 596; $P < .05$). However, perioperative outcomes were not different when comparing PCT with laparoscopic cholecystectomy. In contrast, a study using the US Nationwide Inpatient Sample from 2000-2014 analyzed 200 915 patients aged 65 years or older with acute cholecystitis.[62] Patients who underwent PCT placement had a higher mortality rate compared with patients who underwent cholecystectomy (4.7% vs 1.2%, respectively; $P < .001$), had higher postprocedural bleeding (17.1% vs 9.5%; $P < .001$), had a higher infection rate (13.3% vs 4.5%; $P < .001$), and had a longer hospital length of stay (mean, 1.25 days [95% CI, 1.14-1.37 days]).[62]

In summary, PCT should be used infrequently to treat acute cholecystitis. A PCT may be more beneficial for patients with acalculous cholecystitis, but if laparoscopic cholecystectomy is feasible, current evidence suggests there may be no significant differences in outcomes between PCT and laparoscopic cholecystectomy for patients with acalculous cholecystitis.

Limitations

This review has limitations. First, only English-language studies were included. Second, the literature search may have missed some relevant studies. Third, there was no formal evaluation of the quality of the included studies.

Conclusions

Acute cholecystitis, typically due to gallstone obstruction of the cystic duct, affects approximately 200 000 people in the US annually. In most patient populations, laparoscopic cholecystectomy, performed within 3 days of diagnosis, is the first-line therapy for acute cholecystitis.

ARTICLE INFORMATION

Accepted for Publication: February 7, 2022.

Author Contributions: Dr Charles had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Gallaher.
Administrative, technical, or material support: All authors.

Conflict of Interest Disclosures: None reported.

Disclaimer: Dr Charles is an Associate Editor of *JAMA*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Additional Contributions: We thank Charlotte Smith, a second-year medical student at the University of North Carolina School of Medicine, for her original artistic rendering of the pathogenesis of acute cholecystitis.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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